

or more of ddATP, ddCTP, ddGTP, ddTTP or ddUTP.

Claim 68 (new): A method according to claim 64, wherein the terminators comprise arabinoside triphosphates.

Claim 69 (new): A method according to claim 64, wherein each of the detectable labels is an isotopically labeled moiety, a chromophore, a fluorophore, a protein moiety, or a moiety to which an isotopically labeled moiety, a chromophore, a fluorophore, or a protein moiety can be attached.

Claim 70 (new): A method according to claim 64, wherein each of the different detectable labels is a different fluorophore.

Claim 71 (new): A method according to claim 64, wherein the primer-extension reaction medium further comprises pyrophosphatase.--

R E M A R K S

A. Summary of the Invention

Broadly, in one aspect, the present invention concerns a method of determining the identity of one or more nucleotide basis at a plurality of specific positions in one or more nucleic acid molecules of interest. The method includes the step of treating a sample comprising the nucleic acid molecules of interest if the nucleic acid molecules are double stranded so as to obtain unpaired nucleotide bases spanning the specific positions. Alternatively, a sample of the nucleic acid of interest may be used directly if the nucleic acid molecules are single stranded. The method of the invention includes the step of contacting the sample with a plurality of different oligonucleotide primers. Each different oligonucleotide primer hybridizes under high stringency hybridization conditions to a corresponding different stretch of nucleotide bases present in the nucleic acid molecules of interest which is immediately adjacent to the specific position of a nucleotide base to be identified with that oligonucleotide primer, so as to form a duplex such that the nucleotide base to be identified is the first unpaired base of the nucleic acid

molecule of interest immediately downstream of the 3' end of the primer. Each different oligonucleotide primer comprises a corresponding different affinity moiety. The oligonucleotide primer comprising the affinity moiety is capable of hybridizing with a nucleic acid template and undergoing a nucleic acid template-dependent primer extension reaction with terminator of a terminator reagent. The affinity moiety permits affinity separation of the extended oligonucleotide primer from the terminator reagent. The method of the invention includes the further step of contacting the duplexes with a terminator reagent which includes four different terminators of a nucleic acid template dependent primer extension reaction. The terminator reagent is free of dATP, dCTP, dGTP, and dTTP. Each terminator comprises a different detectable label corresponding to the terminator. One of the terminators is complementary to a nucleotide base to be identified by each of the oligonucleotide primers. The contacting is carried out in a primer extension reaction medium under conditions sufficient to permit a template dependent primer extension reaction, which incorporates the complimentary terminator onto the 3' end of each of the different oligonucleotide primers to thereby extend the 3' end of each of the primers by one terminator. The method of the invention further includes the step of affinity separating the respective extended oligonucleotide primers from the primer extension reaction medium by causing each of the extended oligonucleotide primers to contact an affinity group attached to a solid support. The affinity group is complementary to the affinity moiety incorporated in the oligonucleotide primer. Finally, the method of the invention includes the step of determining the presence and identity of the nucleotide base at each of the respective specific positions in the one or more nucleic acid molecules of interest by detecting the detectable label of the terminator incorporated at the 3' end of each of the affinity separated extended oligonucleotide primers.

B. Summary of the Outstanding Office Action

In the Office Action of 20 September 2002, it was noted that the subject application contained disclosures of nucleotide sequences. It was asserted that the application

failed to comply with the requirements of 37 CFR 1.821 concerning the form of sequence listing in a patent application.

Claims 60 through 63 inclusive of the subject application were rejected under 35 USC §112, first paragraph, with the assertion that the claims contained subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. It was stated that claims 60 through 63 were directed to a method in which either one or more unique oligonucleotide primers were attached to a unique affinity moiety which specifically binds to a discrete position on a solid support or a plurality of unique oligonucleotide primers are attached to discrete positions of a solid support and then the target nucleic acid is added to form a duplex and extension occurs on the immobilized primers. It was stated that claim 63 further included a step of sorting the extended primers by affinity capture. It was asserted that the specification did not provide support for such concepts.

In the outstanding Office Action, claims 60 through 64 inclusive were rejected under 35 USC §112, second paragraph with the assertion that the claims were indefinite for assertedly failing to particularly point out and distinctly claim subject matter which the applicants regarded as the invention. It was asserted that the recitation of “discrete position” and “defined positions” in claims 60 through 63 made the claims unclear as to whether each primer or affinity moiety was attached at a specific and unique location on a solid support or whether a discrete position included a spot on a dot blot. With respect to claim 64, the recitation “each different oligonucleotide primer incorporates a corresponding different affinity moiety which permits polymerase extension of the oligonucleotide primer with terminators of a terminator reagent” was cited. It was asserted that it was unclear as to what was intended to be meant by the expression “primer incorporates.” It was asserted that it was unclear as to what was intended to be meant by the primer “permitting” polymerase extension. While it was recognized that the specification taught that the presence of an affinity moiety did not affect the 3’ extension reactions, it was

asserted that the specification did not clarify what was intended to be meant by a primer, per se, permitting polymerase extension.

C. Summary of the Present Amendments
and Request for Reconsideration

In the present reply, the specification has been amended to provide sequence identification numbers in compliance with 37 CFR 1.821-1.824. A paper A computer diskette containing the nucleotide sequences of the application in computer readable form accompanies the present reply.

Claim 64 has been amended to define with greater particularity that which the applicants regard as the invention.

New claims 65 through 71 inclusive have been added in the present response. The new claims find support, for example, in the application as originally filed at page 27, lines 19 through 24, page 9, lines 23 through 31, and page 18, lines 4 through 16. It is submitted that new claims 65 through 71 inclusive do not constitute new matter.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. Nucleotide Sequence Listings

Pursuant to 37 CFR 1.821(c), the attorneys for the applicants submit herewith a paper copy of a sequence listing which identifies the nucleotide sequences set forth in the subject application. The accompanying sequence listing is written out on four pages in the format specified in 37 CFR 1.822 and 1.823. Please amend the subject application to incorporate the accompanying sequence listing as separately numbered pages following the last page of the specification, page 46, and before the claims of the application. The accompanying sequence listing incorporates no new matter with respect to the application as originally filed.

In accordance with 37 CFR 1.824, the attorneys for the applicants also submit herewith the sequence listing for the application in computer readable form on a floppy disk. The sequence listing was prepared under "MS-Windows" operating system and is IBM PC/XT/AT compatible. The sequence listing information recorded in computer readable form submitted herewith on floppy disk is identical to the written sequence listing submitted herewith.

E. The Rejection Under 35 U.S.C. §112, First Paragraph

As recognized in the outstanding Office Action, the specification of the subject application as originally filed disclosed, for example, at page 29, line 31 through page 30, line 3 that more than one oligonucleotide could be separated from a terminator reagent and analyzed simultaneously if more than one affinity group were used. It is submitted that a person of ordinary skill in the art would have recognized that if more than one oligonucleotide was to be analyzed simultaneously in time, the several oligonucleotides would have to be analyzed at different places. Analyzing more than one affinity separated oligonucleotide at the same time at the same place would have been expected to give rise to interference among the analyses. A person of even only ordinary skill in the art would have appreciated from the specification of the application as filed without exercising inventive faculties that analysis of multiple affinity-separated oligonucleotides could be carried out simultaneously in time as disclosed in the specification, if the oligonucleotides were separately affinity separated at distinct positions.

According to *Webster's Ninth New Collegiate Dictionary*, among the definitions of the verb "sort" is "to arrange according to characteristics: CLASSIFY." It is submitted that the term "sort" is properly descriptive of the process of separately affinity separating more than one oligonucleotide at corresponding distinct positions, which, for the reasons discussed in the preceding paragraph, a person of only ordinary skill in the art would have understood the specification of the subject application as filed to have disclosed. It is submitted, therefore, that claim 63 of the application, which calls for sorting extended primers by affinity capture by affinity moieties attached to a solid support at defined positions, was fully supported in the specification of the subject application as originally filed.

For the reasons set forth above, it is submitted that the subject matter of claims 60 through 63 inclusive was amply described and fully supported in the specification of the subject application as filed. The rejection of claims 60 through 63 inclusive in the outstanding Office Action under 35 U.S.C. § 112, first paragraph, was without justification and should be withdrawn.

F. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the outstanding Office Action, the expressions “discrete position” and “defined positions” were cited in connection with the rejection of claims 60 through 63 inclusive under 35 U.S.C. § 112, second paragraph. Claim 60 specifies that each unique oligonucleotide primer has a unique affinity moiety which specifically binds to a discrete position on a solid support. Claim 62 calls for attaching a plurality of unique oligonucleotide primers to discrete positions of a solid support. Claim 63 calls for attaching a plurality of affinity moieties to a solid support at defined positions. It is submitted that a person of ordinary skill in the art with the specification of the subject application at hand would have readily understood claims 60 through 64 inclusive in their entirety, including the references to discrete positions or defined positions. The references to discrete positions and defined positions are clear and unambiguous, particularly in the context of the methods of claims 60 through 63.

Although it is submitted that claim 64 as originally filed was completely clear and definite and would have been readily understood by a person of ordinary skill in the art, claim 64 has been amended in the present reply with the comments in the outstanding Office Action in mind. It is submitted that claim 64 particularly as amended meets the standards of 35 U.S.C. § 112, second paragraph.

For the reasons set forth above, it is submitted that the rejection of claims 60 through 64 of the subject application under 35 U.S.C. § 112, second paragraph, was without justification and should be withdrawn.

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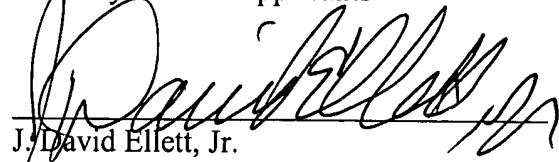
G. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended meet the standards of 35 U.S.C. Section 112, first and second paragraphs, and are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

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